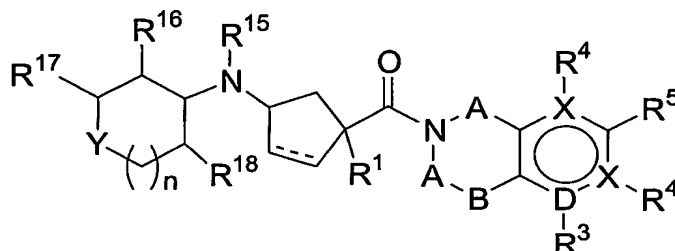


What is claimed is:

1. A compound of formula I:



I

wherein:

A, B, X, and D are defined as follows:

A is independently selected from the group consisting of $-CR^8R^8-$, $-CO-$, $-NR^8-$ and $-O-$,

where R^8 is independently selected from hydrogen, C_{1-6} alkyl, C_{0-4} alkylCOR¹¹ and

where R^{11} is selected from the group consisting of hydroxy, hydrogen, C_{1-6} alkyl, $-O-$, C_{1-6} alkyl, benzyl, phenyl and C_{3-6} cycloalkyl, where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, C_{1-3} alkyl, C_{1-3} alkoxy, $-CO_2H$, $-CO_2-C_{1-6}$ alkyl and trifluoromethyl;

B is selected from the group consisting of $-CR^2R^2-$, $-O-$, $-SO-$, $-SO_2-$, $-NSO_2R^{14}-$, $-NCOR^{13}-$, $-NCONR^{12}R^{12}-$ and $-CO-$,

where R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, fluoro, hydroxy, heterocycle, $-NHCOR^{13}$, $-NHCO_2R^{14}$, and $-O-C_{1-6}$ alkyl,

where R¹² is selected from the group consisting of hydrogen, C₁₋₆ alkyl, benzyl and phenyl, and C₃₋₆ cycloalkyl

5 where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl,

10 where R¹³ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl,

15 where R¹⁴ is selected from the group consisting of hydroxy, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl, and

20 where said heterocycle is unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, -COR¹¹, C₁₋₃alkyl, C₁₋₃alkoxy and trifluoromethyl;

25 X is carbon or nitrogen;

D is carbon, or when one of B, X and D is not CR²R², carbon, and carbon, respectively, D is a carbon or nitrogen;

30 provided that A, B, X, and D cannot be simultaneously CR⁸R⁸, CR²R², CR⁴, and CR³, respectively, and that D can only be nitrogen when at least one of A, B, or X is not CR⁸R⁸, CR²R², or CR⁴, respectively, where R⁸, R², R⁴, and R³ are defined below;

35 Y is selected from the group consisting of -O-, -NR¹²-, -S-, -SO-, -SO₂-, and -CR¹¹R¹¹-, -NSO₂R¹⁴-, -NCOR¹³-, -NCONR¹²R¹²-, -CR¹¹COR¹¹-, -CR¹¹OCOR¹³- and -CO-;

R¹ is selected from the group consisting of hydrogen, -C₁₋₆alkyl, -C₀₋₆alkyl-O-C₁₋₆alkyl, -C₀₋₆alkyl-S-C₁₋₆alkyl, -(C₀₋₆alkyl)-(C₃₋₇cycloalkyl)-(C₀₋₆alkyl), hydroxy, heterocycle, -CN, -NR¹²R¹², -NR¹²COR¹³, -NR¹²SO₂R¹⁴, -COR¹¹, -CONR¹²R¹², and phenyl,

5

where said alkyl and said cycloalkyl are unsubstituted or substituted with 1-7 substituents where said substituents are independently selected from the group consisting of:

- (a) halo,
- (b) hydroxy,
- (c) -O-C₁₋₃alkyl,
- (d) trifluoromethyl,
- (f) C₁₋₃alkyl,
- (g) -O-C₁₋₃alkyl,
- (h) -COR¹¹,
- (i) -SO₂R¹⁴,
- (j) -NHCOCH₃,
- (k) -NHSO₂CH₃,
- (l) -heterocycle,
- (m) =O, and
- (n) -CN, and

10

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where said phenyl and heterocycle are unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, -COR¹¹, C₁₋₃alkyl, C₁₋₃alkoxy and trifluoromethyl;

25

R³ is selected from the group consisting of:

- (a) hydrogen,
- (b) C₁₋₃alkyl, optionally substituted with 1-3 fluoro,
- (c) -O-C₁₋₃alkyl, optionally substituted with 1-3 fluoro,
- (d) hydroxy,
- (e) chloro,
- (f) fluoro,
- (g) bromo,
- (h) phenyl,
- (i) heterocycle and
- (j) nothing, O, or hydrogen, when the Z bonded to R³ is nitrogen);

30

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R⁴ is selected from the group consisting of:

40

- (a) hydrogen,

- 5 (b) C₁₋₃alkyl, optionally substituted with 1-3 fluoro,
 (c) -O-C₁₋₃alkyl, optionally substituted with 1-3 fluoro,
 (d) hydroxy,
 (e) chloro,
 (f) fluoro,
 (g) bromo,
 (h) phenyl,
 (i) heterocycle, and
 10 (j) nothing, O, or hydrogen, when the Z bonded to R⁴ is nitrogen;

R⁵ is selected from the group consisting of:

- 15 (a) C₁₋₆alkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro and optionally substituted with hydroxyl,
 (b) -O-C₁₋₆alkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,
 (c) -CO-C₁₋₆alkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,
 (d) -S-C₁₋₆alkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,
 20 (e) -pyridyl, which is unsubstituted or substituted with one or more substituents selected from the group consisting of: halo, trifluoromethyl, C₁₋₄alkyl, and COR¹¹,
 (f) fluoro,
 (g) chloro,
 (h) bromo,
 25 (i) -C₄₋₆cycloalkyl,
 (j) -O-C₄₋₆cycloalkyl,
 (k) phenyl, which is unsubstituted or substituted with one or more substituents selected from the group consisting of: halo, trifluoromethyl, C₁₋₄alkyl, and COR¹¹,
 30 (l) -O-phenyl, which is unsubstituted or substituted with one or more substituents selected from the group consisting of: halo, trifluoromethyl, C₁₋₄alkyl, and COR¹¹,
 (m) -C₃₋₆cycloalkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,
 35 (n) -O-C₃₋₆cycloalkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,
 (o) -heterocycle,
 (p) -CN and
 40 (q) -COR¹¹;

R¹⁵ is selected from the group consisting of:

- (a) hydrogen and
(b) C₁₋₆alkyl, which is unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of halo, hydroxy, -CO₂H, -CO₂C₁₋₆alkyl, and -O-C₁₋₃alkyl;

5

R¹⁶ is selected from the group consisting of:

- (a) hydrogen,
(b) C₁₋₆alkyl, where alkyl is unsubstituted or substituted with 1-6 substituents where the substituents are chosen from the group: fluoro, C₁₋₃alkoxy, hydroxy, -COR¹¹,
(c) fluoro,
(d) -O-C₁₋₃alkyl, where alkyl is unsubstituted or substituted with 1-3 fluoro, and
(e) C₃₋₆ cycloalkyl,
(f) -O-C₃₋₆cycloalkyl,
(g) hydroxy,
(h) -COR¹¹ and
(i) -OCOR¹³,
or R¹⁵ and R¹⁶ may be joined together via a C₂₋₄alkyl or a C₀₋₂alkyl-O-C₁₋₃alkyl chain to form a 5-7 membered ring;

10

15

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R¹⁷ is selected from the group consisting of:

- (a) hydrogen,
(b) C₁₋₆alkyl, where alkyl may be unsubstituted or substituted with 1-6 substituents where said substituents are chosen from the group: fluoro, C₁₋₃alkoxy, hydroxy, -COR¹¹,
(c) COR¹¹,
(d) hydroxy, and
(e) -O-C₁₋₆alkyl, where alkyl may be unsubstituted or substituted with 1-6 substituents where said substituents are chosen from the group: fluoro, C₁₋₃alkoxy, hydroxy, -COR¹¹,
or R¹⁶ and R¹⁷ are joined together by a C₁₋₄alkyl chain or a C₀₋₃alkyl-O-C₀₋₃alkyl chain to form a 3-6 membered ring;

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R¹⁸ is selected from the group consisting of:

- (a) hydrogen, and
(b) C₁₋₆alkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,

40

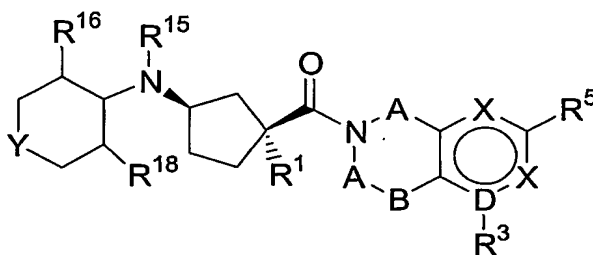
- (c) fluoro,
 (d) -O-C₃₋₆cycloalkyl, and
 (e) -O-C₁₋₃alkyl, where alkyl is unsubstituted or substituted with 1-6 fluoro,
 or R¹⁶ and R¹⁸ are joined together by a C₂₋₃alkyl chain to form a 5-6 membered
 ring, where said alkyl are unsubstituted or substituted with 1-3 substituents where
 said substituents are independently selected from the group consisting of halo,
 hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy,
 or R¹⁶ and R¹⁸ are joined together by a C₁₋₂alkyl-O-C₁₋₂alkyl chain to form a
 6-8 membered ring, where said alkyl are unsubstituted or substituted with 1-3
 substituents where said substituents are independently selected from the group
 consisting of halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and
 C₁₋₃alkoxy,
 or R¹⁶ and R¹⁸ are joined together by a -O-C₁₋₂alkyl-O-chain to form a 6-7
 membered ring, where said alkyl are unsubstituted or substituted with 1-3
 substituents where said substituents are independently selected from the group
 consisting of halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and
 C₁₋₃alkoxy;

n is selected from 0, 1 and 2;

the dashed line represents a single or a double bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

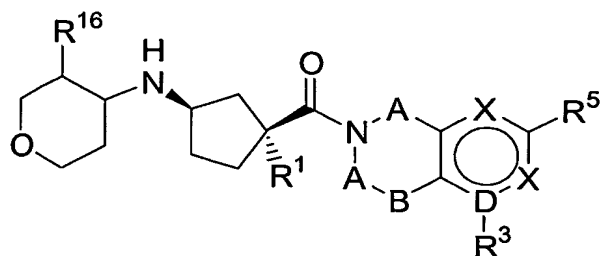
2. A compound of Claim 1 of formula Ia:



Ia

wherein R¹, R³, R⁵, R¹⁵, R¹⁶, R¹⁸, A, B, D, X, and Y are defined in Claim 1,
 and pharmaceutically acceptable salts and individual diastereomers thereof.

3. A compound of Claim 1 of formula Ib:

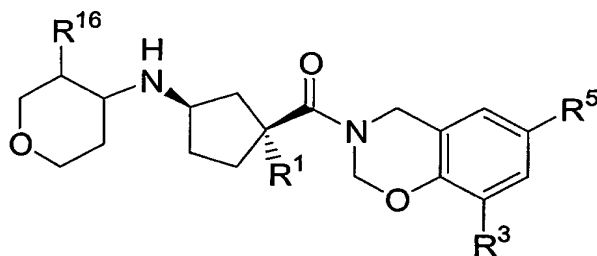


Ib

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wherein R¹, R³, R⁵, R¹⁶, A, B, D, and X are defined in Claim 1, and pharmaceutically acceptable salts and individual diastereomers thereof.

4. A compound of Claim 1 of formula Ic:



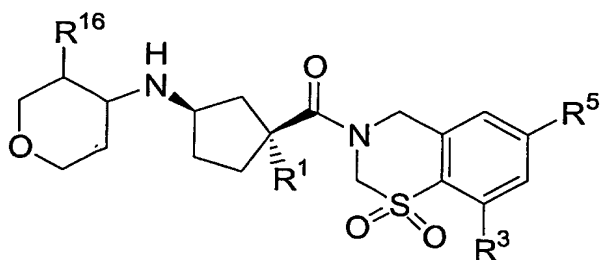
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Ic

wherein R¹, R³, R⁵ and R¹⁶ are defined in Claim 1, and pharmaceutically acceptable salts and individual diastereomers thereof.

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5. A compound of Claim 1 of formula Id:

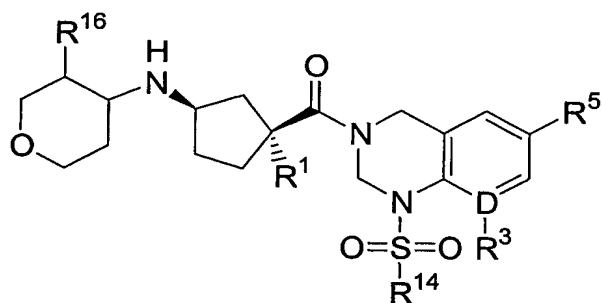


Id

wherein R^3 , R^5 , and R^{16} are defined in Claim 1 and pharmaceutically acceptable salts and individual diastereomers thereof.

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6. A compound of Claim 1 of formula Ie:

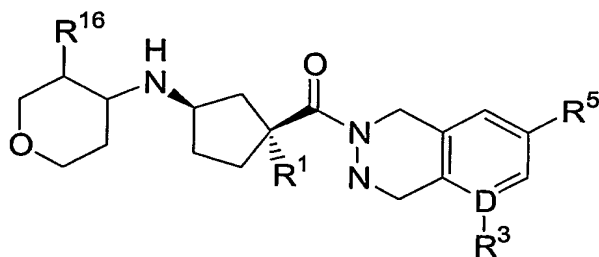


Ie

wherein R^3 , R^5 , R^{16} , and D are defined in Claim 1 and pharmaceutically acceptable salts and individual diastereomers thereof.

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7. A compound of Claim 1 of formula If:

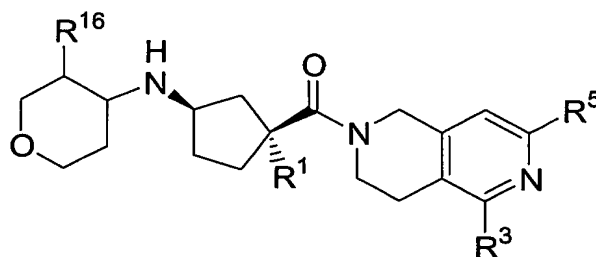


If

wherein R^3 , R^5 , R^{16} , and D are defined in Claim 1 and pharmaceutically acceptable salts and individual diastereomers thereof.

5

8. A compound of Claim 1 of formula Ig:

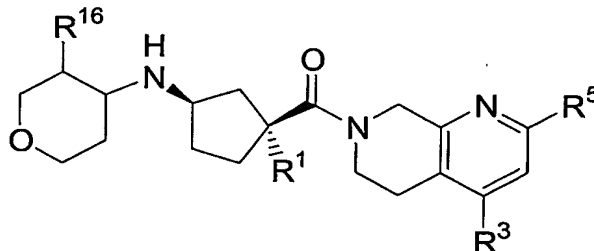


Ig

wherein R^3 , R^5 , and R^{16} are defined in Claim 1 and pharmaceutically acceptable salts and individual diastereomers thereof.

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9. A compound of Claim 1 of formula Ih:



Ih

wherein R^3 , R^5 , and R^{16} are defined in Claim 1 and pharmaceutically acceptable salts and individual diastereomers thereof.

15

10. A compound of Claim 1 wherein Y is selected from the group consisting of: -O-, -CH₂-, -S-, -SO-, and -SO₂-.

20

- consisting of
11. A compound of Claim 1 wherein R^1 is selected from the group
- (1) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with 1-6 substituents where said substituents are independently selected from the group consisting of:
- (a) halo,
- (b) hydroxy,
- (c) $-O-C_{1-3}$ alkyl,
- (d) trifluoromethyl and
- (e) $-COR^{11}$,
- (2) $-C_{0-6}$ alkyl- $O-C_{1-6}$ alkyl-, which is unsubstituted or substituted with 1-6 substituents where said substituents are independently selected from the group consisting of
- (a) halo,
- (b) trifluoromethyl and
- (c) $-COR^{11}$,
- (3) $-(C_{3-5}$ cycloalkyl)- $(C_{0-6}$ alkyl), which is unsubstituted or substituted with 1-7 substituents where said substituents are independently selected from the group consisting of
- (a) halo,
- (b) hydroxy,
- (c) $-O-C_{1-3}$ alkyl,
- (d) trifluoromethyl and
- (e) $-COR^{11}$, and
- (4) phenyl or heterocycle which is unsubstituted or substituted with 1-3 substituents where said substituents are independently selected from the group consisting of
- (a) halo,
- (b) hydroxy,
- (c) $-O-C_{1-3}$ alkyl,
- (d) trifluoromethyl, and
- (e) $-COR^{11}$.
12. A compound of Claim 11 wherein R^1 is C_{1-6} alkyl which is unsubstituted or substituted with 1-5 substituents where said substituents are independently selected from the group consisting of:
- (a) hydroxy, and
- (b) fluoro.

13. A compound of Claim 12 wherein R^1 is selected from the group consisting of:

- 5 (a) isopropyl,
(b) $-\text{CH}(\text{OH})\text{CH}_3$, and
(c) $-\text{CH}_2\text{CF}_3$.

14. A compound of Claim 1 wherein D is nitrogen and R^3 is nothing, hydrogen, or oxygen.

10 15. A compound of Claim 14 wherein D is nitrogen and R^3 is nothing or hydrogen.

16. A compound of Claim 15 wherein D is nitrogen and R^3 is nothing.

15 17. A compound of Claim 1 wherein D is carbon and R^3 is selected from:

- 20 (a) hydrogen
(b) halo
(c) hydroxy
(d) C_{1-3} alkyl, where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from the group consisting of fluoro, and hydroxy,
25 (e) $-\text{COR}^{11}$,
(f) $-\text{CONR}^{12}\text{R}^{12}$,
(g) heterocycle,
(h) $-\text{NR}^{12}-\text{SO}_2-\text{NR}^{12}\text{R}^{12}$,
(i) $-\text{NR}^{12}-\text{SO}_2-\text{R}^{14}$,
30 (j) $-\text{SO}_2-\text{NR}^{12}\text{R}^{12}$,
(k) -nitro and
(l) $-\text{NR}^{12}\text{R}^{12}$.

18. A compound of Claim 16 wherein D is carbon and R^3 is selected from the group consisting of:

- 35 (a) fluoro,
(b) trifluoromethyl and
(c) hydrogen.

19. A compound of Claim 18 wherein D is carbon and R³ is
(a) fluoro or
(b) hydrogen.
- 5 20. A compound of Claim 1 wherein X is nitrogen and R⁴ is absent,
hydrogen or oxygen.
21. A compound of Claim 20 wherein X is nitrogen and R⁴ is absent.
- 10 22. A compound of Claim 20 wherein X is carbon and R⁴ is selected from
the group consisting of:
- (a) hydrogen,
(b) trifluoromethyl and
15 (c) halo.
23. A compound of Claim 22 wherein X is carbon and R⁴ is hydrogen.
- 20 24. A compound of Claim 1 wherein R⁵ is selected from the group
consisting of
- (a) C₁₋₃alkyl substituted with 1-6 fluoro,
(b) chloro,
(c) bromo,
(d) -O-phenyl, which is unsubstituted or substituted with one or more
25 substituents selected from the group consisting of: halo and
trifluoromethyl,
(e) phenyl, which is unsubstituted or substituted with one or more
substituents selected from the group consisting of: halo and
trifluoromethyl, and
30 (f) -O-C₁₋₃alkyl substituted with 1-6 fluoro.

25. A compound of Claim 24 wherein R^5 is selected from the group consisting of:
- 5 (a) trifluoromethyl,
(b) trifluoromethoxy,
(c) bromo, and
(d) chloro.
- 10 26. A compound of Claim 25 wherein R^5 is selected from trifluoromethyl and trifluoromethoxy.
27. A compound of Claim 1 wherein R^{15} is hydrogen or methyl.
- 15 28. A compound of Claim 1 wherein R^{16} is selected from the group consisting of:
- (a) hydrogen,
(b) C_{1-3} alkyl, which is unsubstituted or substituted with 1-6 fluoro,
(c) $-O-C_{1-3}$ alkyl,
(d) fluoro, and
20 (e) hydroxy.
29. A compound of Claim 28 wherein R^{16} is selected from the group consisting of:
- 25 (a) hydrogen,
(b) trifluoromethyl,
(c) methyl,
(d) methoxy,
(e) ethoxy,
(f) ethyl,
30 (g) fluoro, and
(h) hydroxy.

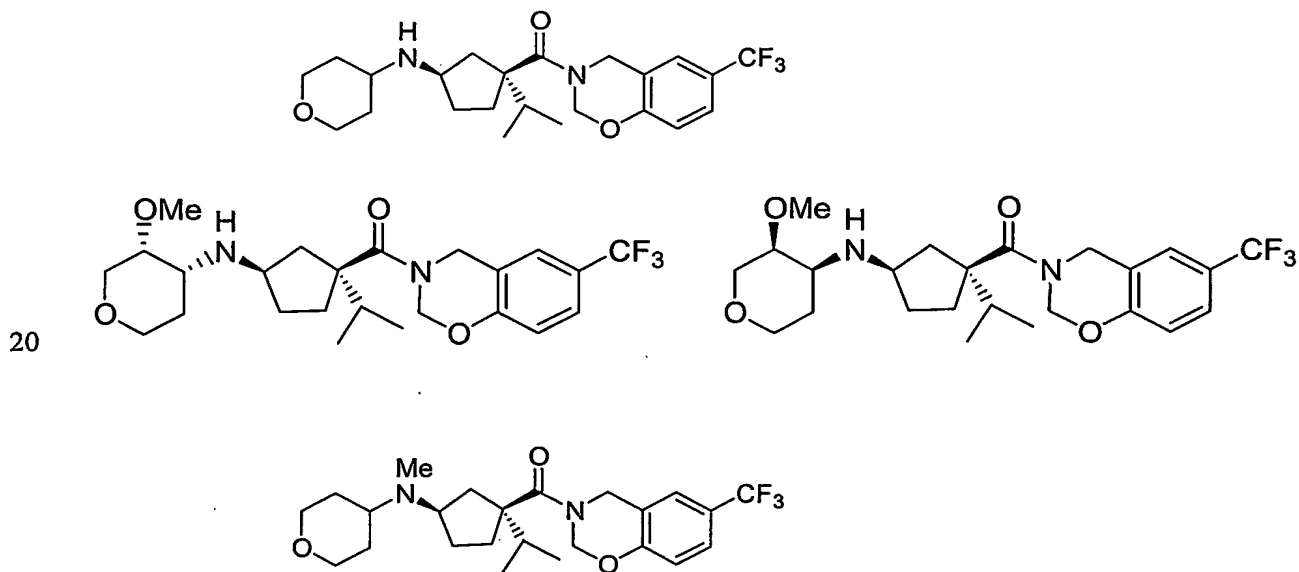
30. A compound of Claim 29 wherein R¹⁶ is selected from the group consisting of:

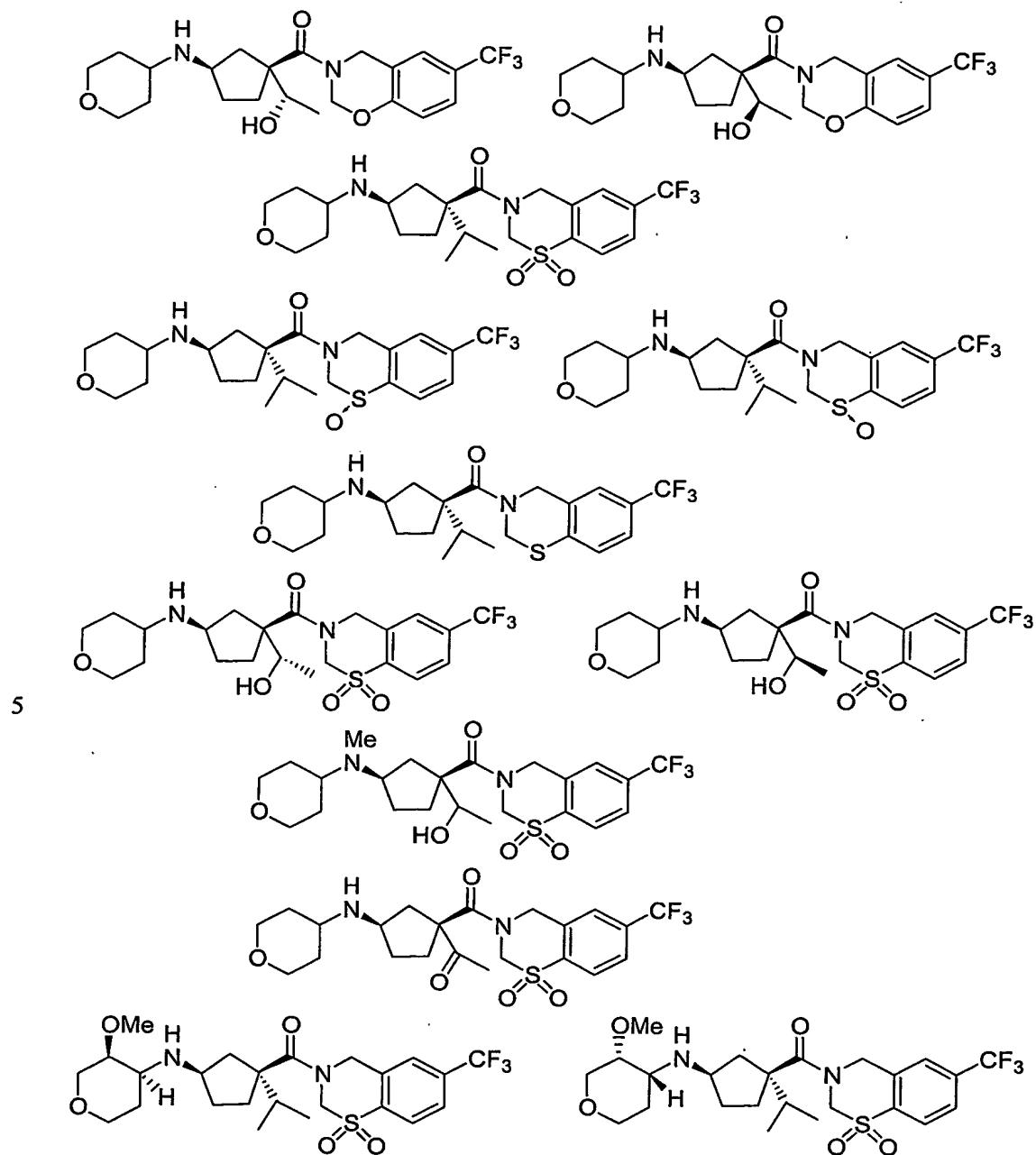
- 5 (a) hydrogen,
(b) methyl, and
(c) methoxy.

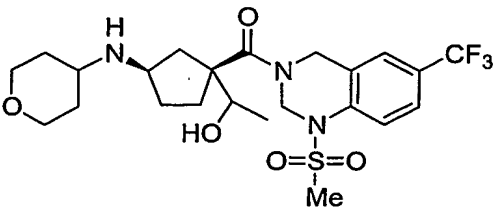
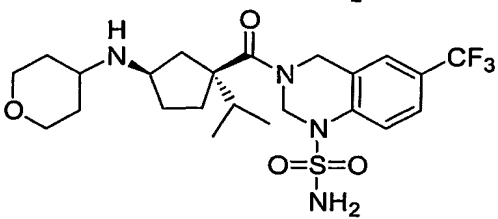
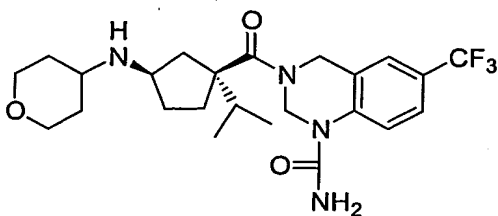
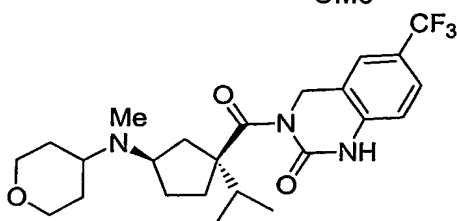
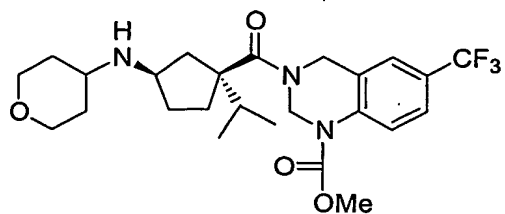
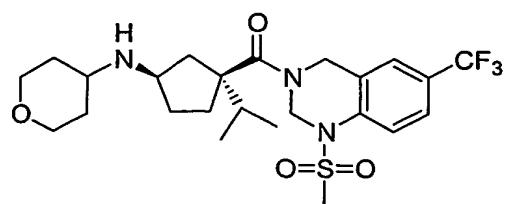
31. A compound of Claim 1 wherein R¹⁸ is selected from the group consisting of:

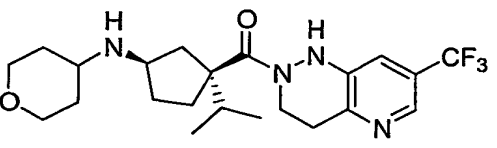
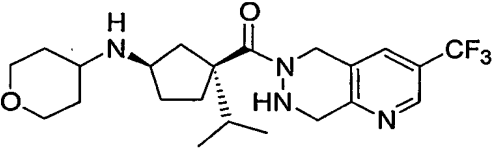
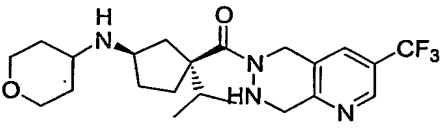
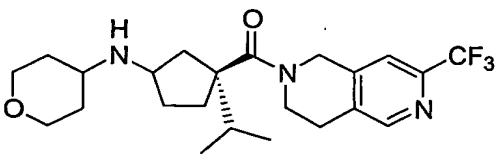
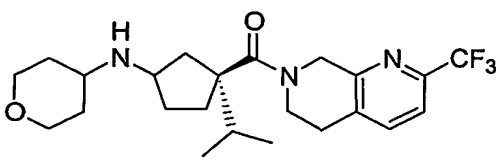
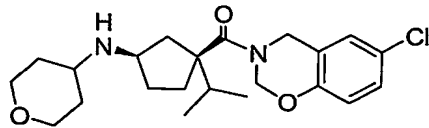
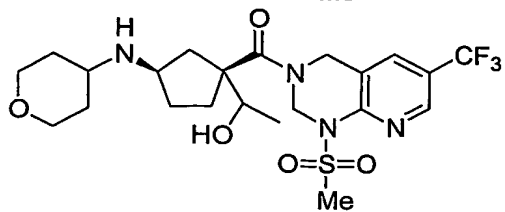
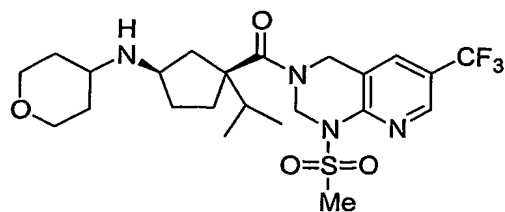
- 10 (a) hydrogen,
(b) methyl, and
(c) methoxy.

32. 15 of: 32. One or more compounds of Claim 1 selected from the group consisting

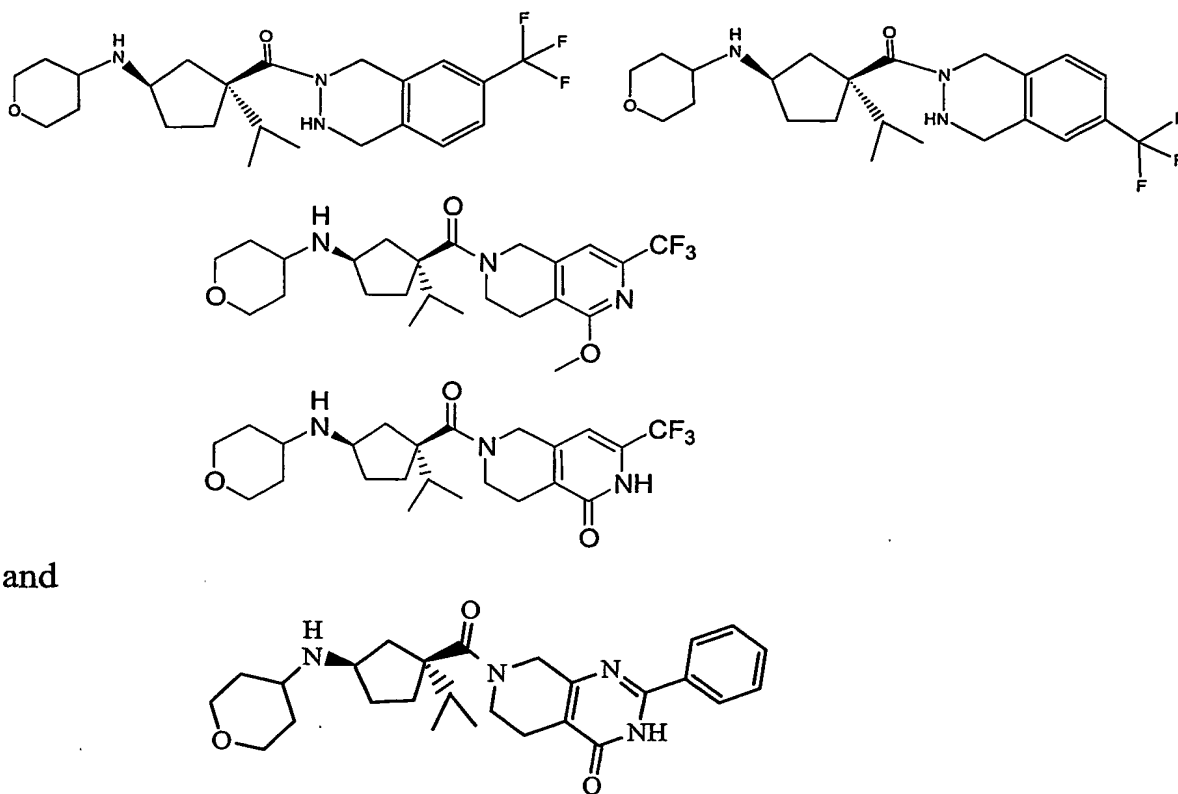








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33. A compound of Claim 1 wherein R¹⁶ and R¹⁸ are joined together by a -CH₂CH₂- chain or a -CH₂CH₂CH₂- chain to form a cyclopentyl ring or a cyclohexyl ring.

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34. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

35. A method for modulation of chemokine receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

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36. A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of the compound of Claim 1.

37. A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of the compound of Claim 1.